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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FULBRIGHT & JAWORSKI L.L.P.
Melissa W. Acosta
Suite 5100
1301 McKinney
Houston, TX 77010-3095

EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	9

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/827,688	ORSON ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *5 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-15,17-21 and 23-42* is/are rejected.

7)☒ Claim(s) *6 and 22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed on 1/21/03 in Paper No. 8 has been entered.

Claims 1-42 are pending in the present application.

Applicant's election without traverse of the invention of Group I (claims 1-42) in Paper No. 5 is acknowledged. Applicants further elected without traverse genes associated with an infectious disease with HIV as a pathogenic viral genome, gastrointestinal mucosal surface and subcutaneous administration as the elected species. Therefore, claims 5 and 16 are withdrawn from further consideration because they are drawn to non-elected species. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Claims 1-4, 6-15 and 17-42 are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Following is a new ground of rejection necessitated by Applicants' amendment.

Claim Rejections - 35 USC § 112

Amended claims 23-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention essentially for the same reasons already set forth in the previous Office Action.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Amended claims 23-27 are drawn to a method of treating a condition in a mammal by administering to the mammal the DNA composition of claim 12. With respect to the elected species of the DNA composition comprising a polynucleotide sequence encoding an antigen wherein the polynucleotide sequence is a fragment of an HIV genome, and when read in light of the specification the instant claims are basically drawn to a method for protecting and/or treating a mammal from HIV infection by administering the DNA composition of the present invention into the mammal via any parenteral route (with subcutaneous administration as the elected species) or to any mucosal surface (with gastrointestinal muscosal surface as the elected species). The instant specification is not enabled for this claimed invention for the following reasons.

(1) The breadth of the claims. With respect to the elected species, the instant claims encompass a method for protecting (within the scope of treating a condition, e.g., susceptible to HIV infection) and/or treating (e.g., preventing, slowing, stabilizing and stopping the progression of the condition) any mammal from HIV infection by

administering the DNA composition of the present invention into the mammal via any parenteral route or to any mucosal surface.

(2) The state and the unpredictability of the prior art. The nature of the instant claims falls within the realm of the genetic vaccination art that at the effective filing date of the present application remains unpredictable with respect to obtaining prophylactic and therapeutic effects. Chattergoon et al. (FASEB J. 11:753-763, 1997) state "Though DNA vaccines have shown promise in animal models and have raised hopes, the technology is considered an emerging technology" (column 1, paragraph 2, page 762). More recently, Leitner et al. (Vaccine 18:765-777, 2000) state "Although genetic vaccines have been significantly improved, they may not be sufficiently immunogenic for therapeutic vaccination of patients with infectious disease or cancer in clinical trials" (Abstract, page 765). Leitner et al. also listed several variable factors affecting the immunogenicity of genetic vaccines. These include: the structure of the plasmid backbone, amount of plasmid delivered, expression levels of the antigen, age and strain of the particular species, target tissue, and route of immunization among others (See Table 1, page 767). Additionally with respect to the elected species of using a DNA composition comprising a nucleotide sequence encoding an antigen, wherein the nucleotide sequence is a fragment of an HIV viral genome, the sole purpose for a method of treating a condition in a mammal for such a DNA composition is for attaining prophylactic and therapeutic effects in humans due to the specific infection of HIV in a human host. At the effective filing date of the present application, there is no known effective DNA composition for treating HIV infection in humans. Additionally, McCluskie

et al. (Mol. Med. 5:287-300, 1999) state "[I]t is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa. Therefore, it is difficult to predict from mouse studies the potential of a new vaccine for humans. In fact, in those human trials that have carried out, none of the DNA vaccines induced the strong immune responses that had been seen in mice with the same vectors" (col. 2, last paragraph, page 296).

(3) The amount of direction or guidance provided. In light of the state of the prior art, the instant specification fails to provide sufficient guidance for a skilled artisan on how to use the DNA composition of the presently claimed invention for obtaining any prophylactic and/or therapeutic effects in treating any condition encompassing a host of infectious diseases caused by pathogenic virus, bacterium, fungus and protozoa, cancer and autoimmune disease, particularly for treating an HIV infectious condition. Although the exemplification showing that upon intravenous and oral administration of an expression plasmid vector bound to a macroaggregated albumin (MAA)-polyethyleneimine (PEI) conjugate into a mammal (mice and macaques) both systemic and mucosal immune responses were elicited, however it is unclear whether these induced immune responses are sufficient or effective to prevent or eradicate or treat a host of infectious diseases, cancers and autoimmune diseases, and particularly HIV infection, let alone the contemplated prophylactic and/or therapeutic effects could be attained by any parenteral route of administration or via the administration at any mucosal surface. There is no correlation between the observed induced immune responses in mice and macaques reported in the present application with any

prophylactic and therapeutic effects achieving in humans against HIV infection because an effective DNA vaccine for which still remains elusive. The instant specification fails to provide sufficient guidance, particularly in the absence of any relevant *in vivo* example (part of guidance) for a skilled artisan on how to achieve any prophylactic and/or therapeutic effects in preventing or treating HIV infection in any mammal using the DNA composition of the presently claimed invention. As such, it would have required undue experimentation for a skilled artisan to make and use the method as claimed with respect to the elected species.

Moreover, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient direction or guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological and genetic vaccine arts, and the breadth of the claims, it would have required undue experimentation to make and use the instantly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-27 and 32-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24-27 recite the limitation "the vaccine" in line 1 of claims 24 and 26. There is insufficient antecedent basis for this limitation in the claim. There is no recitation of any vaccine in amended claim 23 from which claims 24-27 are dependent upon. Therefore, the metes and bounds of the claims are not clearly determined.

In claim 32 and its dependent claims, it is unclear what is encompassed by the phrase "the second vector comprises a cytokine expression vector". How does an expression vector contain in itself another expression vector? Clarification is requested because the metes and bounds of the claims are not clearly determined.

Claim Rejections - 35 USC § 102

Claims 1, 7-8, 42 and newly amended claims 12, 20-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Kircheis et al. (Gene therapy 4:409-418, 1997; IDS) for essentially the same reasons already set forth in the previous Office Action.

Kircheis et al. disclose the preparation of DNA complexes of ligand-polyethylenimine (PEI) conjugates for transfection of cultured neuroblastoma Neuro 2A cells, melanoma B16 or H225 cells, erythroid leukemic K562 cells and T cell leukemia Jurkat E6.1 cells, wherein the ligand is transferrin or CD3 antibody (see abstract and Materials and methods section). During the synthesis of transferrin-PEI or antiCD3-PEI conjugates, transferrin and antiCD3 molecules would be linked together in addition to

them being linked to PEI molecules (see pages 416-417 for their synthesis procedures). As transferrin and antiCD3 molecules are proteins and they are bound together via the modification (qualified as an aggregate according to the definition in the instant specification on page 8, second last paragraph). The DNA utilized in the study of Kircheis et al. include a plasmid pCMVL coding for the *Photinus pyralis* lucifease gene, the plasmid pCMVβ coding for galatosidase, the plasmid pWS2m coding for murine IL-2, all of which under the control of the cytomegalovirus enhancer/promoter (page 416, col. 2, under the section titled "Cells and vectors"). Galacosidase, luciferase and murine IL-2 are capable of provoking an immune response in certain hosts, and thereby they are antigens. Kircheis et al. further teach that ligand-conjugated polyethylenimines mediate efficient and enhanced transfection of cultured tumor cells (see Figs. 1-4), and these may be promising vectors for receptor-specific gene delivery (page 409, col. 2, last sentence).

Accordingly, Kircheis et al. anticipate the instant claims.

Response to Arguments

Applicants' arguments related to the above rejection in the amendment filed on 1/21/03 in Paper No. 8 (pages 5-7) have been fully considered.

Applicants argue mainly that the conjugations performed by Kircheis et al. would not yield protein aggregates as suggested by Examiner, and that the resulting conjugate taught by Kircheis et al. is a single transferrin conjugated to PEI. Therefore, Kircheis et al. do not anticipate the instant claims.

Applicants' arguments are respectfully found to be unpersuasive because under the conjugation conditions of Kircheis et al., there are no reasonable scientific reasons why the free amine groups present in the transferrin molecules would not react (intra and/or intermolecular interactions) with the aldehyde groups or between the aldehyde groups (intra and/or intermolecular interactions) present in the transferrin molecules generated as a result of the sodium periodate reaction. As such, the crosslinked transferrin molecules in the transferrin-PEI conjugates having various molar ratios (2, 4 and 8) of transferrin to PEI, would fall within the scope of an aggregated protein as defined broadly by the present application as a protein that has been combined to form a large amorphous particle. To further support Examiner's position, Parsons (U.S. Patent 4,069,352) teaches that sodium periodate which causes cleavage of gem diols of proteins which contain sugar residues (transferrin is a glycoprotein) to generate dialdehydes which in turn cross-link with each other (col. 2, lines 61-66). Examiner further notes that the addition of sodium borohydride is for the stabilization of the intermolecular and/or intramolecular crosslinks formed. Therefore, the teachings of Kircheis et al. meet every limitation of the instant claims.

Claim Rejections - 35 USC § 103

Claims 1-4, 7-11, 28-31 and newly amended claims 12-15, 17-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston et al. (U.S. Patent No. 5,703,057) in view of Kircheis et al. (Gene therapy 4:409-418, 1997; IDS) for essentially the same reasons already set forth in the previous Office Action.

Johnston et al. disclose a composition comprising expression vectors encoding antigens prepared from gene sequences derived from a pathogenic virus, including HIV, for expression in a mammalian cell and a method for generating an immune response into a mammal using the same via various modes of administration including parenteral as well as mucosal routes (see Summary of Invention, cols. 2-8; col. 11). Johnston et al. further teach that mammalian genes fused to the pathogen DNA can facilitate expression in the mammalian cell, specifically human growth hormone, ubiquitin, signal sequences and others (col. 5, lines 19-29). Johnston et al. disclose that fusion of nonmammalian pathogen sequences to mammalian genes increases the amount of antigen available to the immune system due to increasing antigenic recognition or targeting to components in the cell.

Johnston et al. do not teach that the expression vectors encoding antigens prepared from gene sequences derived from a pathogenic virus, including HIV, for expression in a mammalian cell are bound to an aggregated protein-polycationic polymer conjugates.

However, at the effective filing date of the present application Kircheis et al. disclose the preparation of DNA complexes of ligand-polyethylenimine (PEI) conjugates for gene delivery, specifically using transferrin or CD3 antibody as a cell-binding ligand (see abstract). During the synthesis of transferrin-PEI or antiCD3-PEI conjugates, transferrin and antiCD3 molecules would be linked together in addition to them being linked to PEI molecules (see pages 416-417 for their synthesis procedures). As transferrin and antiCD3 molecules are proteins and they are bound together via the

modification (qualified as an aggregate according to the definition in the instant specification on page 8, second last paragraph). Kircheis et al. note that ligand-conjugated polyethylenimines mediate efficient and enhanced transfection of cultured tumor cells (see Figs. 1-4), and these may be promising vectors for receptor-specific gene delivery (page 409, col. 2, last sentence). It is further noted that the cell-binding transferrin ligand binds to a receptor expressed on the surface of most proliferating cells.

Accordingly, at the time of the instant invention it would have been obvious and within the scope of skill for an ordinary skilled artisan to modify the method of Johnston et al. by preparing the composition comprising expression vectors encoding antigens prepared from gene sequences derived from a pathogenic virus, including HIV, bound to a ligand-PEI conjugate for antigen expression in a mammalian cell, particularly immune effector cells, at a target tissue or site to induce an immune response in a mammal based on the teachings of Kircheis et al.

An ordinary skilled artisan would have been motivated to make this modification because as taught by Kircheis et al., ligand-conjugated polyethylenimines mediate an efficient and enhanced transfection, and that these are promising vectors for receptor-specific gene delivery. An enhanced cell transfection rate would be advantageous for induction of a host immune response specific to an antigen due an increased in the amount of antigen available to the host immune system.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the amendment filed on 1/21/03 in Paper No. 8 (page 7) have been fully considered.

Applicants argue mainly that Kircheis et al. reference does not teach protein aggregates, and therefore it does not cure the deficiency of the Johnstone reference. Additionally, there is no suggestion in Kircheis et al. or Johnstone that protein aggregates would be desirable.

Applicants' arguments are respectfully found to be unpersuasive for the same reasons already set forth in the Response to Applicants' arguments for the rejection of claims 1, 7-8, 42 and newly amended claims 12, 20-21 above. Moreover, Kircheis et al. clearly teach that ligand-conjugated polyethylenimines mediate an efficient and enhanced transfection, and that these are promising vectors for receptor-specific gene delivery. An enhanced cell transfection rate would be advantageous for induction of a host immune response specific to an antigen due an increased in the amount of antigen available to the host immune system, which is the motivation for one skilled in the art to modify the method of Johnstone.

Amended claims 32-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston et al. (U.S. Patent No. 5,703,057) in view of Kircheis et al. (Gene therapy 4:409-418, 1997; IDS) and Weiner et al. (U.S. 6,348,449) for essentially the same reasons already set forth in the previous Office Action.

The teachings of Johnston et al. and Kircheis et al. have been discussed above. However, none of the references teaches a method for inducing an immune response in a mammal by co-administering into the mammal two expression vectors, both bound to an aggregated protein-polycationic polymer conjugate wherein the first expression vector comprises a promoter polynucleotide sequence operatively linked to a polynucleotide sequence encoding an antigen and the second vector comprises a cytokine expression cassette, or the a method of inducing an immune response in a mammal by administering an expression vector coding an antigen and a cytokine bound to an aggregated protein-polycationic polymer conjugate.

However, at the effective filing date of the present application, Weiner et al. already teach that for immunization applications, the genetic construct contains nucleotide sequences that encode a target protein and further include genes for proteins which enhance the immune response against such target protein. Examples of such genes are those which encode cytokines and lymphokines such as GM-CSF, IL-2, PDGF, IL-1, and others (line 60 of col. 5 continues to line 4 of col. 6, and see the claims).

Accordingly, at the time of the instant invention it would have been obvious and within the scope of skill for an ordinary skilled artisan to further modify the method of Johnston et al. and Kircheis et al. by further incorporating a cytokine expression vector bound to the same aggregated protein-polycationic polymer conjugate or using an expression vector encoding both an antigen and a cytokine that is bound in an aggregated protein-polycationic polymer conjugate. It would also have been obvious

and within the scope of skill for an ordinary skilled artisan to use the same or different promoters for expressing the sequences encoding an antigen and a cytokine as long as the antigen and cytokine are expressed.

An ordinary skilled artisan would have been motivated to make the above modification because as taught by Weiner et al., the co-expression of cytokines and lymphokines such as GM-CSF, IL-2 and others can enhance an immune response against the desired target protein.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the amendment filed on 1/21/03 in Paper No. 8 (pages 7-8) have been fully considered.

Applicants argue mainly that none of the cited references teach protein aggregates, and that any of the references suggests that a protein aggregate is desirable as a DNA delivery method.

Applicants' arguments are respectfully found to be unpersuasive for the same reasons already set forth above.

Conclusions

Claims 6 and 22 are objected because they are dependent on the rejected claims 1 and 12, respectively; and that they would be allowable if they are rewritten in independent form.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER